REMARKS

No new matter has been added by virtue of these amendments and new claims. Their entry is respectfully requested.

Claims 50 through 68 are added from co-pending application Ser. No. 08/903,830 (corresponding to claims 13 through to 30, and 33), now abandoned. These claims of U.S. Ser. No. 08/903,830 were allowed in a Notice of Allowance dated May 21, 2003. U.S. Ser. No. 08/903,830 has the same specification as the present application.

Claims 68 through 96 are added from co-pending application No. 09/034,464 (corresponding to claims 1 through 8 and 15 through to 35), now abandoned. U.S. Ser. No. 08/903,830 has the same specification as the present application.

Support for the new claims is found throughout the application. For example, construction of mutants is described on 7, lines 2 to 35; and page 16, lines 4 to 34 through to page 20, lines 1 to 35. Types of mutations, e.g. nonsense, deletion etc, are described on page 8, lines 1 through 16 and figures 4 and 5; Preferred double mutations are described on page 8, lines 17 to 21; characterization of mutants is described on page 21 lines 1 to 21 through to page 29, lines 1 to 26. B and T cell responses to the mutants are described on page 40, lines 1 to 16 through to 51 lines 1 to 9.

Applicants appreciate the acknowledgement of patentable subject matter at least in claims 16 and 22. Claim 16, which is directed to the treatment of herpetic stromal keratitis, has been amended to make it an independent claim. The treatment of herpetic stromal keratitis subject matter of claim 22 has been incorporated into claim 18 from which it depended.

Claims 12-15 and 17-21 are rejected under 35 U.S.C. § 112, first paragraph. It is respectfully submitted that the amendment overcomes this basis for rejection.

Claims 31 and 36 are rejected under 35 U.S.C. § 112, second paragraph. Applicants respectfully traverse.

Applicant's have amended the claims without changing there scope to make explicit that which was implicit. That is, the mutations in the mutant herpesvirus renders the mutant "replication defective" at the genomic level. Applicants have also amended the claims to clarify that the "protective immune response" is induced by encoding heterologous genes. Applicants respectfully request that this rejection be withdrawn.

Claims 31, 36, and 41 are rejected under 35 U.S.C. § 103(a) over Inglis et al (WO 92/05263) in view of McCarthy et al (*Journal of Virology* 63:18-27, 1989). Applicants respectfully traverse.

First, Inglis is **not** prior art to the instant invention. The instant invention claims priority to U.S.S.N. 07/922,921 filed 7/31/1992. Applicants point out that, on page 3 lines 11 to 24 of U.S.S.N. 07/922,921 (hereinafter referred to as '921), the preferred embodiments explicitly state that "the mutation is in the gene encoding HSV-1 **ICP27** or HSV-1 **ICP8 or the corresponding homologs** of those genes **in a non-HSV-1 herpesvirus**." (page 3, lines 12 to 15; emphasis added). These mutants are well characterized as seen from the results in figures 1 to 17 (see figure description also, page 4 through to line 23 on page 9). The mutant herpes viruses, as disclosed in '921 must also satisfy certain criteria, for example, "incapable of producing viable progeny" (page 11, lines 13-14); "they should be capable of inducing a protective immune response" (page 11, lines 15 to 16). In fact, '912 teaches that the incapacity of the herpesvirus mutant to produce viable progeny, is due to the mutant herpesvirus **inability to replicate** (see page 11, lines 16 to 23; emphasis added). The application, further discloses that herpesvirus mutants which satisfy these criteria include those "which contain mutated ICP27 or ICP8 genes." (see page 11, lines 24 to 25). The claims of '912 are drawn to vaccines with the aforementioned properties.

The claims of the instant application are, therefore, **fully supported by, both the instant specification and the specification of '912 filed July 31, 1992.** Both specifications have as preferred embodiments, mutated ICP27 or ICP8 genes (See, for example, the instant application page 4, lines 1-8; page 11, lines 1-9; page 12, lines 29-31; page 14, lines 4-31, through to page 15 lines 1-7).

Thus, Inglis WO 92/05263, **is not prior art** to the instant application and a rejection based on a 35 U.S.C. § 103(a) is improper.

However, Applicants further submit that the present invention is contrary to the teachings of the combination of cited references, Inglis, and McCarthy. Claims of the instant application have been amended to clarify that the invention is directed to mutant herpes viruses with mutations in the **early genes** such that the **viral genome is not replicated and infectious virus** is therefore not produced.

The Examiner alleges on page 6, last paragraph that McCarthy teaches "a gene encoding a protein essential for production of infectious virus," and when combined with Inglis "one would expect reasonable success." Applicants do not teach a herpesvirus mutant that is infectious. In fact, Inglis in view of McCarthy would teach away from the instant invention. Applicants claims are directed to herpesvirus mutants for vaccine purposes, wherein the mutants have mutations in at least **one or two early** genes, **one of which is an immediate early gene (ICP27)**, (see page 6, lines 11-29; page 22, lines 10-26 through to page 38, lines 11-14 describing the construction of the ICP 27 mutant) which render the double mutant herpesvirus **incapable of replication (i.e. non-replicating viral genome)**, yet remain immunogenic. Furthermore, the claims are drawn to a viral genome replication defective mutated herpesvirus **expressing heterologous proteins**.

The combination of references, Inglis, and McCarthy teach away from using immediate early gene mutants and Applicants submit that it would not have been obvious to one of ordinary skill in the art to use the double mutants of the invention because Inglis teaches that ***replication*** of the attenuated virus ***is not interrupted in the early phase***. In fact, Inglis teaches that replication of viral genome is essential to produce viral particles. On page 7, lines, 11-15, Inglis states that :

> "Firstly, a selected gene is inactivated within the virus genome, usually by creating a specific deletion. This gene will be involved in the **production of infectious virus**, but preferably **not preventing replication of the viral genome**." (Emphasis added).

Inglis et al, continually stresses that for the virus mutant to act as vaccine requires replication of the viral genome. (See page 8, lines 12-18; page 10, lines 17-20). Inglis does not teach or suggest that a non-replicating virus can be used as a vaccine. In contrast, applicants invention is directed to a herpesvirus mutant wherein the viral genome is non-replicating. Applicants surprisingly have discovered that, even though their herpesvirus mutants **do not replicate their viral genome**, are highly effective as vaccines.

The Examiner makes note of Inglis, page 10, wherein the Examiner alleges that "In theory, any gene encoding an essential protein should be a target for this approach to the creation of attenuated viruses." However, Inglis *et al* stress (see page 9, lines 6 to 12), that for cytomegalovirus (Human Herpes Virus 5) "the selected gene may be one (***other than the Immediate Early gene***) that effectively prevents viral genome replication *in vivo*, since the Immediate Early gene which is produced prior to viral genome replication (***and indeed is essential for it***) is ***highly immunogenic***." (Emphasis added).

Inglis *et al*, teaches, on page 8, lines 22 - 25, that "**[t]he** deleted or inactivated **gene** is preferably one involved as **late** as possible in the viral cycle, so as to provide as

many viral proteins as possible in vivo for generating an immunogenic response." (Emphasis added).

Thus, one of ordinary skill in the art would have been taught by Inglis et al. that the Immediate Early gene must be functioning to provide an infectious virus capable of replicating its genome in order to produce an immunogenic response.

Inglis also teaches on page 10, lines 13-20:

> "In ***practice*** however, the selection of the gene will be driven by a number of considerations.
> 1. The gene should preferably be one which is required ***later in infection***. Thus, ***replication*** of the attenuated virus ***is not interrupted in the early phase***." (Emphasis added).

Thus, Inglis teaches away from using herpes viruses with a mutation in the immediate early gene, since Inglis teaches that such herpesvirus early gene mutations would **not** be immunogenic **and** require functioning early genes for replication of the virus to produce **many viral proteins** as possible in vivo for generating an immunogenic response." (*Id.*).

In contrast, Applicants herein surprisingly have discovered that their disclosed herpesvirus mutants with mutations in the early genes **are** highly immunogenic, **do not replicate their genome**, **and** can still be used for vaccine purposes. Most importantly, Applicants teach, in contrast to Inglis et al., that a heprsevirus mutant that does **not** replicate its genome is **highly effective** as a vaccine. This teaching of Applicants is wholly unexpected from a consideration of Inglis et al.

McCarthy also teaches the **importance of early genes in the life cycle of the virus** and each reference reports attempts to examine potential functional roles of these proteins in the cell. More specifically, McCarthy suggests "an essential role for ICP27 in the modulation of early and late gene expression at the transcriptional level." (Abstract,

page 18). The McCarthy reference does not suggest even using the deletions for vaccine purposes because it is a study in the potential mechanisms of these proteins.

Thus, Inglis in view of McCarthy teach away from the use of viral vaccines with deletions in the early genes. Further, the combination of references, also are silent regarding the use of **double** early gene mutants as vaccines; and are also silent regarding any suggestion that a herpesvirus mutant with such mutations such that it **does not replicate its genome could be effective as a vaccine.**

Yet, as Applicants have shown, herpesvirus mutations that result in a virus that does not replicate its genome provide a highly effective as a vaccine. (See for example, pages 40, lines 4-16, through to page 55, lines 1-2).

Further, in contrast to Inglis and McCarthy, Applicants not only teach the use of mutations in the early genes but teach the use of mutations in **at least two early** genes (see, for example page 8, lines 1-28), **and** which express heterologous proteins. Construction of the mutant herpesviruses of the invention, expressing heterologous proteins is disclosed on page 11, lines 4-35 through to page 12, lines 1- 33. The combination of the above-references fail to teach or suggest that the mutant (immediate early/early) herpes viruses **that expresses heterologous proteins** would indeed be useful as vaccines. Especially so, in view of the fact that these vaccine virus disclosed by Applicants are **incapable of replicating their genomes**.

Thus, the combination of Inglis, and McCarthy does not teach or suggest Applicants' invention.

In view thereof, reconsideration and withdrawal of the rejection is requested.

"Claims 12-17, 31, 36 and 41 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-14 of co-pending Application No. 09/034,464."

Applicants respectfully traverse.

"Claims 12-22, 31, 36 and 41 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 13-34 of co-pending Application No. 08/903,830."

Applicants respectfully traverse.

To expedite examination of the present application, co-pending Application Ser. No. 08/903,830 and co-pending Application Ser. No. 09/034,464 have been expressly abandoned. Copies of the notices of express abandonment are attached hereto. Because these applications are terminated there no longer are any double patenting issues. It is respectfully submitted that the rejection under the judicially created doctrine of obviousness-type double patenting should be withdrawn.

It is respectfully submitted that the subject application is in a condition for allowance. Early and favorable action is requested. If any issues remain, the Examiner is requested to call Applicants' undersigned attorney to expedite the resolution of such issues.

Respectfully submitted,

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